

# Exhibit A

**UNITED STATES DISTRICT COURT  
DISTRICT OF NEW JERSEY**

MITSUBISHI TANABE PHARMA  
CORPORATION, JANSSEN  
PHARMACEUTICALS, INC., JANSSEN  
PHARMACEUTICA NV, JANSSEN  
RESEARCH AND DEVELOPMENT, LLC,  
and CILAG GMBH INTERNATIONAL,

Plaintiffs,

v.

ZYDUS PHARMACEUTICALS (USA)  
INC.,

Defendant.

Civil Action No. 17-5005 (RMB)(JS)  
(consolidated)

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**OPENING INFRINGEMENT EXPERT REPORT  
OF BERNHARDT L. TROUT, PH.D.**

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I, Bernhardt Trout, Ph.D. submit the following report on behalf of Mitsubishi Tanabe Pharma Corporation, Janssen Pharmaceuticals, Inc., Janssen Research and Development, LLC, and Cilag GMBH International in this action.

**I. EXPERT QUALIFICATIONS**

**A. Area of Expertise**

1. Based on my experience and qualifications, I consider myself an expert in the fields of crystalline and pharmaceuticals materials testing, crystal nucleation and growth, crystal engineering, X-ray crystallography, solid-state chemistry, physical chemistry, chemical engineering, and pharmaceutical development and manufacturing. Accordingly, I believe that I am more than competent to express the opinions set forth below.

**B. Educational Background**

2. I obtained a Bachelor of Science degree and a Master of Science degree in Chemical Engineering from the Massachusetts Institute of Technology (“MIT”) in 1990.

3. I obtained a Ph.D. in Chemical Engineering from the University of California at Berkeley in 1996. In addition, I performed post-doctoral research at the Max-Planck-Institut für Festkörperforschung in Stuttgart, Germany from 1996-1997.

**C. Relevant Professional Experience**

4. I am currently the Raymond F. Baddour, ScD, (1949) Professor of Chemical Engineering at MIT. I am also currently the Director of the Society, Engineering, and Ethics Program (SEE).

5. In 1998, I became an Assistant Professor of Chemical Engineering at MIT. In 2003, I became an Associate Professor of Chemical Engineering at MIT, and in 2008, I became a full Professor of Chemical Engineering at MIT. During the period from 2008-2014, I was the Co-Chair of Chemical and Pharmaceutical Engineering Singapore-MIT Alliance Program.

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During the period from 2007-2019, I was the Director, and founding Director, of the Novartis-MIT Center for Continuous Manufacturing.

6. I have taught more than 1000 students in undergraduate and graduate university chemical engineering courses, including courses in Thermodynamics, Chemical Reactor Engineering, Kinetics of Biological and Chemical Systems, Chemical Kinetics and Reactor Design, Process Engineering Laboratory, Molecular Computational Methods in Chemical Engineering, and Chemical Engineering Design Module. I have also taught and supervised graduate students (at both the Masters and Ph.D. level), post-doctoral researchers, and research scientists with a primary emphasis on pharmaceutical development and manufacturing research. The research of these supervisees often encompassed crystalline and pharmaceutical materials testing, crystal nucleation and growth, crystal engineering, and X-ray crystallography.

7. In my own laboratory, I perform X-ray powder diffractometry (“XRPD”)<sup>1</sup>, Infrared (“IR”) Spectroscopy, Raman Spectroscopy, Ultraviolet-Visible (“UV-Vis”) Spectroscopy, Thermogravimetric Analysis (“TGA”), Differential Scanning Calorimetry (“DSC”), and Karl-Fischer Titration, in addition to a wide variety of other analytical methods. In shared laboratories at MIT, I also perform single-crystal X-ray Diffractometry (“sc-XRD”), solid state nuclear magnetic resonance (“ssNMR”) and a variety of other analytical methods.

8. I have consulted widely for industry, particularly in the fields of pharmaceutical development and manufacturing, including crystallization. I also work closely with the United States Food and Drug Administration (“FDA”) and was a consultant for the FDA Advisory Committee for Pharmaceutical Science and Clinical Pharmacology. In addition, I work with other regulatory agencies, in particular the European Medicines Agency and Japan’s

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<sup>1</sup> XRPD can also be referred to as PXRD, powder X-ray diffraction, or powder XRD.

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Pharmaceutical and Medical Devices Agency. I also work with the United States Pharmacopeia and was recently a member of their Expert Panel on Quality Standards for Pharmaceutical Continuous Manufacturing.

9. I am a member of various professional societies, including the American Institute of Chemical Engineers, the American Chemical Society, and the America Association of Pharmaceutical Scientists.

10. I have published over 200 papers in peer reviewed journals in the field of crystalline and pharmaceuticals materials testing, crystal nucleation and growth, crystal engineering, X-ray crystallography, solid-state chemistry, physical chemistry, chemical engineering, and pharmaceutical development and manufacturing. I regularly give invited lectures, including keynote and plenary lectures to academics, professional organizations, regulatory bodies, including the FDA, and industry.

11. For a complete list of my professional experiences, publications and lectures, please see my curriculum vitae attached hereto as Exhibit 1.

**D. Awards and Honors**

12. I received the National Science Foundation Graduate Research Fellowship from 1991 through 1994. From 1996-1997, I received the Max-Planck Institute Fellowship for Biophysical Chemistry. In 2000-2004, I received the National Science Foundation Faculty Early Career Development (“CAREER”) Award. I received the Ford Motor Company Young Investigator Award in 2001. In 2011, I received the Impact Award from the Computational Molecular Science and Engineering Forum of the American Institute of Chemical Engineers. In 2012, my continuous manufacturing technology led to the Manufacturing Technology Runner-Up for the Wall Street Journal Technology Innovation Award. In 2014, I received the Counsel for Chemical Research Collaboration Award. I received the Medicine Maker “Power List”

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award in 2015, 2016, and 2017. In 2015, I received the American Institute of Chemical Engineers Division 15 Plenary Speaking award.

13. For a complete list of my awards and honors, please see my curriculum vitae attached hereto as Exhibit 1.

**E. Other Testimonial Experiences**

14. Exhibit 2 lists all sworn testimonies I have provided within the last four years.

**F. Compensation**

15. I am being compensated at my usual rate of \$900 per hour in connection with this proceeding. My compensation does not depend in any way on the outcome of this litigation.

**II. BASES FOR OPINIONS**

16. The opinions that I express in this report are based on the information and evidence currently available to me. The materials that I considered in forming my opinions set forth in this report are discussed in my report and/or listed in Exhibit 3. I also relied on my general knowledge, experience, and scientific analysis.

**III. OVERVIEW OF OPINIONS**

17. I understand that Defendant Zydus Pharmaceuticals (USA), Inc. (“Zydus”) seeks permission from the FDA to market generic versions of Plaintiffs’ 100 mg and 300 mg Invokana<sup>®</sup> (canagliflozin) drug products and Plaintiffs’ 50 mg/ 500 mg, 50 mg/1000 mg, 150 mg/500 mg and 150 mg/1000 mg Invokamet<sup>®</sup> (canagliflozin/metformin) drug products. Specifically, Zydus submitted Abbreviated New Drug Application (“ANDA”) No. 210541 (“the ’541 ANDA”) for 100 mg and 300 mg canagliflozin tablets (“Zydus’s ’541 ANDA Products”) and ANDA No. 210542 (the ’542 ANDA”) for 50 mg/ 500 mg, 50 mg/1000 mg, 150 mg/500 mg and 150 mg/1000 canagliflozin/metformin tablets (“the ’542 ANDA Products”) (collectively, “Zydus’s ANDA Products”).

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18. I have been asked to consider whether Zydus's ANDA Products infringe claims 1 and 3 of U.S. Patent No. 7,943,582 ("the '582 patent") (Ex. 4). For at least the reasons set forth below, it is my opinion that each of Zydus's ANDA Products infringe claims 1 and 3 of the '582 patent.

19. I am also prepared to serve in a teaching capacity to discuss scientific principles relating to my areas of expertise, as well as the level of ordinary skill in the art at the relevant time(s) and background relating to the issues discussed herein.

**IV. DISCLOSURES REGARDING PROPOSED EXPERT TESTIMONY**

**A. Person of Ordinary Skill in the Art**

20. I have been asked by counsel to use December 4, 2006, the filing date of the provisional application to which the '582 patent claims priority, as the relevant date for my analysis. My opinions would not change if I used December 3, 2007, the non-provisional filing date of the '582 patent, as the relevant date for my analysis.

21. In my opinion, as of either December 4, 2006 or December 3, 2007, a person of ordinary skill in the art ("POSA") would be (a) a person with an advanced degree in chemistry, analytical chemistry, physical chemistry, organic chemistry, pharmaceutical chemistry, medicinal chemistry, or chemical engineering, and with at least two years of experience developing, characterizing, and/or analyzing pharmaceutical compounds and products; or (b) a person with a bachelor's degree in one of those disciplines and several years of practical experience in researching, developing, characterizing and/or analyzing crystals and/or polymorphs in solid state chemistry. I am a person of at least ordinary skill under this definition. The opinions I express in the report are from the viewpoint of a POSA as I have defined it.

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**B. Legal Standards Regarding Patent Infringement**

22. In forming my opinions in this case, I used the following legal standards that were provided to me by counsel.

23. I understand that the plaintiff bears the burden of proving patent infringement by a preponderance of the evidence. That is it is more likely than not that the defendant's product(s) infringe. It is my understanding that the plaintiff must show that the defendant's accused product meets each and every claim limitation properly construed literally.

24. I understand that it is an act of infringement to submit an ANDA for a drug product claimed in a patent. It is my further understanding that in the context of an ANDA, the question for infringement is whether, if the drug product in question were approved based on the ANDA, the manufacture, use, sale, or offer to sell that drug product in the United States would lead to infringement of the patent.

25. I understand that infringement involves a two-step analysis. The first step is determining the proper construction of the asserted claims. I have reviewed the claim constructions that have been adopted in this case, as I discuss below.

26. I understand that the second step in the infringement analysis is to compare the properly construed claims to the accused products. The accused products infringe if they meet every element of a properly construed claim.

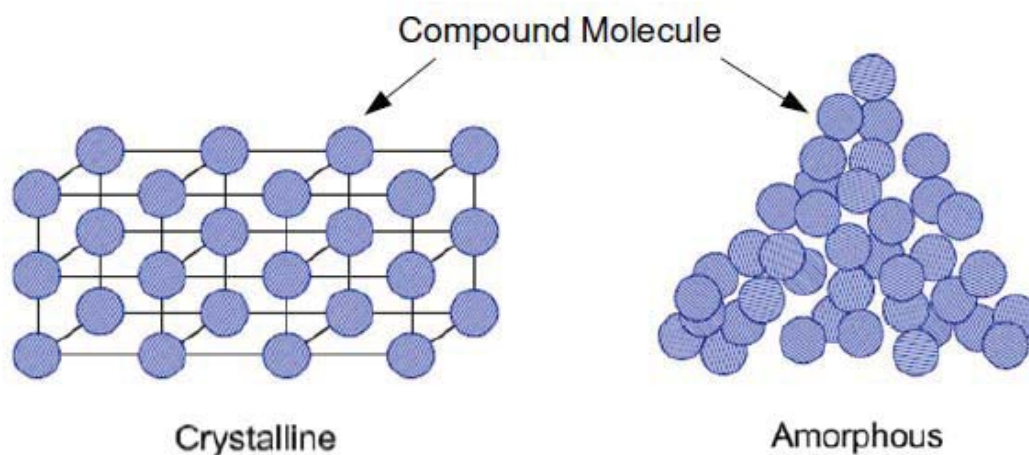
**C. Technology Background**

27. Solid compounds can be amorphous or crystalline, or mixtures of the two. An amorphous solid form is a non-crystalline solid form in which there is no long-range order to the molecules. A crystal or a crystalline solid form is a solid form of a compound in which the molecules are arranged in a three-dimensional structure with regular repeating spatial arrangements among the molecules. A crystalline lattice is the three-dimensional arrangement of

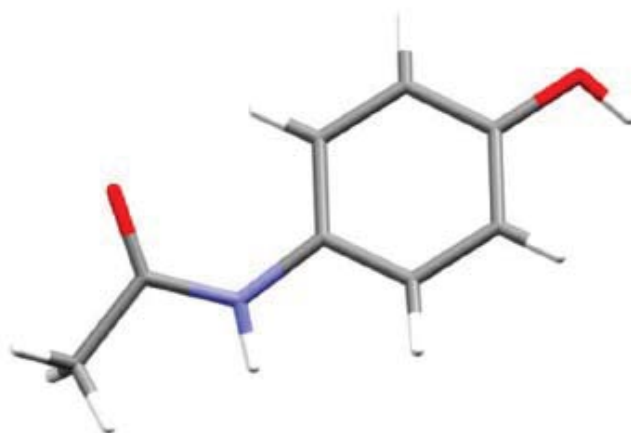


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these molecules within the crystal. The figures below schematically illustrate the arrangement of molecules in a crystalline form and in an amorphous form:



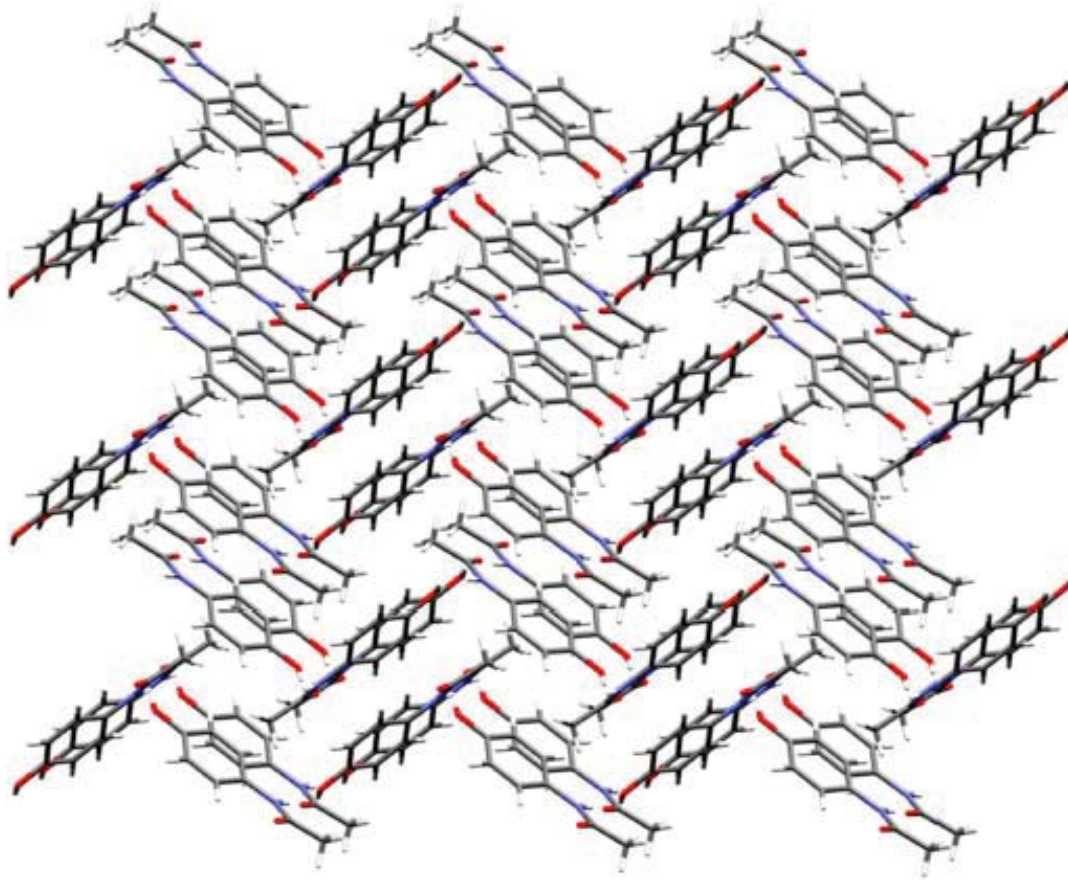
28. I will explain the concepts of crystals and polymorphism using acetaminophen as an example. A single molecule of acetaminophen has the following molecular structure:



**Acetaminophen Molecule**

29. When a sample of acetaminophen is crystallized, the molecules in the sample can arrange themselves into a regularly repeating three-dimensional pattern as shown below:

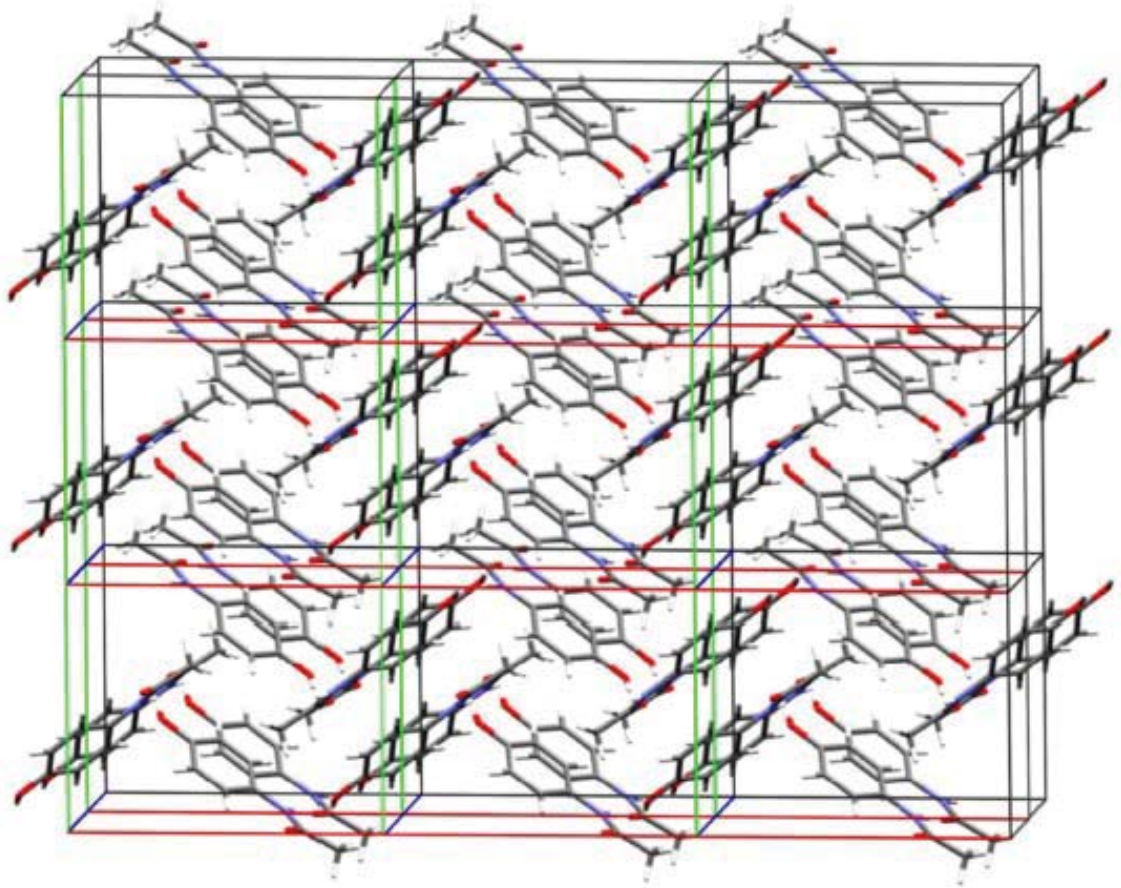
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**Regularly Repeating 3-D Array of Acetaminophen Molecules**

30. This three-dimensional arrangement of molecules is the crystalline lattice in which the molecules are packed in a regular and repeating manner.

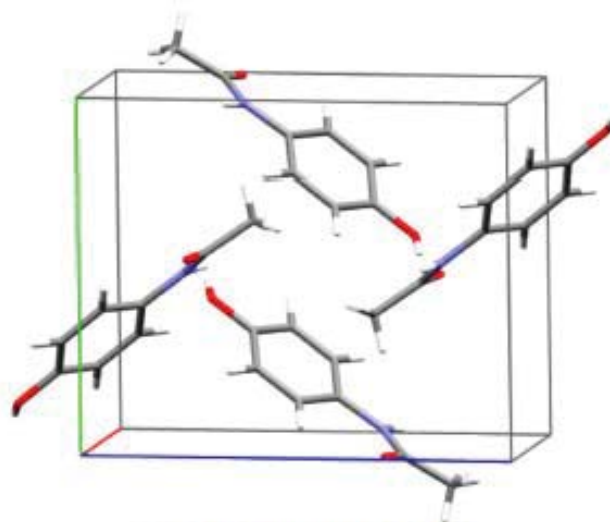
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**Crystal Lattice of Acetaminophen**

31. The smallest repeating unit of a crystalline lattice is known as the unit cell. The crystalline lattice of acetaminophen shown above can also be depicted in terms of the unit cell, as shown below:

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**Acetaminophen Unit Cell**

32. As can be seen in the above figure, the unit cell is a theoretical construct that aids scientists in studying and characterizing crystals. It does not correspond to the shape of individual molecules themselves but to a combination of molecules with specific structures. The ways in which the molecules of the compound (acetaminophen in my example) arrange themselves in space determine the size and shape of the unit cell. Each unit cell is like a brick and the crystal lattice is like a three-dimensional brick structure. A crystalline solid therefore can be described by the shape and size of a single unit cell because its three-dimensional crystal structure is simply a lattice of those unit cells repeating in all three dimensions.

33. Molecules of a compound may arrange themselves in more than one way, which may give rise to different crystalline structures or different crystalline “forms.” Some compounds have no crystalline forms. Other compounds can exist in more than one distinct crystalline form. Polymorphism exists when the same compound exists in more than one crystal form, with each form having a different crystalline lattice. The different crystalline forms are called “polymorphs.”

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34. Some crystalline forms incorporate solvent molecules. Water, acetone, or methanol are examples of solvents that have been identified in specific crystalline lattices of specific compounds.

35. Crystalline forms having solvent molecules and the active compound contained within the repeating structure of the crystal lattice are called solvates. Crystalline forms having water molecules and the active compound contained within the repeating structure of the crystal lattice are often referred to as hydrates. A hydrate is a type of solvate. Crystalline forms that do not contain any water or other solvent are often referred to as “anhydrous” or “unsolvated.”

36. Solvates can have a specific ratio of solvent molecules to molecules of the active compound, and these are called stoichiometric solvates. Solvates can also have a varying ratio of solvent molecules to molecules of the active compound, and these are called non-stoichiometric solvates. Different forms of solvates of a given compound are called “pseudopolymorphs”, where the “pseudo” is added because of the presence of the solvent. However, they are also just called “polymorphs”, and for the purpose of this report, I will use the term “polymorphs” or just “crystalline forms.”

37. Stoichiometric hydrates are named based on the number of water molecules and active compound contained in the repeating structure of the crystal lattice. For example, a crystal form that contains approximately one molecule of water for every molecule of the given compound is referred to as a monohydrate. A crystal form that contains approximately one-half a molecule of water for every molecule of the given compound is referred to a hemihydrate. A hemihydrate can also be referred to as a crystal form having approximately one molecule of water for every two molecules of the given compound, or a 1:2 molar ratio, which is the same as a 0.5:1 molar ratio.



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38. A sample of a given compound may exist as a mixture of different crystalline solid forms or as a mixture of one or more crystalline and amorphous forms.

39. There are many ways to test for the presence of crystals within a sample, including (without limitation) whether the sample exhibits birefringence and whether the sample exhibits an XRPD pattern with defined peaks. Often, regular microscopy can be used to detect the presence of crystals, in addition to differential scanning calorimetry (“DSC”). According to the specification of the ’582 patent, there are several methods for characterizing crystalline forms. (Ex. 4 at 2:52-55.) Crystalline forms can be characterized using well-known techniques such as, but not limited to, XRPD, single-crystal X-ray diffractometry, ssNMR, Raman spectroscopy, infrared spectroscopy, elemental analysis, differential scanning calorimetry (“DSC”), Karl Fischer analysis (“KF”), and thermogravimetric analysis (“TGA”). These methods have been standard since at least 1995 (*See* Ex. 5, Threlfall, *Analyst*, Oct. 1995:120; 2435-2460.)

**1. X-Ray Powder Diffraction**

40. One technique that can be used to identify the crystal structure of a crystalline material and distinguish between different polymorphs of the same material is X-ray diffraction (“XRD”). When XRD is carried out on materials in powder form it can be referred to as X-ray powder diffraction (“XRPD”).

41. XRPD works by measuring the way in which the crystalline structures diffract incident radiation, specifically X-rays, which varies based on the orientation of the molecules within the unit cell. Crystals may diffract X-rays at different “scattering angles” and at different “intensities.” A “scattering angle” is the angle of the incident X-ray beam to the crystalline powder sample, where the scattering of the X-rays is observed and “intensities” is the measure of the number of X-rays that are scattered. Of importance to the patent claims in this case, the

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intensities are measured as a function of scattering angles, typically in terms of two theta (“ $2\theta$ ”).

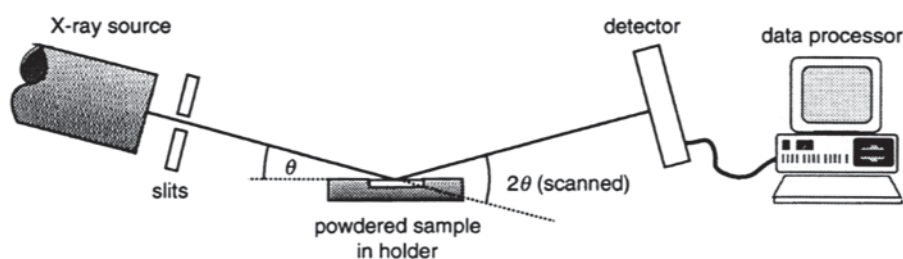
Peaks of those intensities can occur at specific values of  $2\theta$ , which can also be referred to as  $2\theta$

peaks. The instrument used to perform X-ray diffraction is called an X-ray diffractometer.

Powder diffraction data is typically presented as a diffractogram, which is a plot of intensity as a

function of  $2\theta$ . As of December 4, 2006, it was well understood that an observed XRPD peak

may vary within  $\pm 0.2^\circ 2\theta$ . Below is a schematic of XRPD:



**Figure 3.1** Schematic drawing of a modern  $2\theta$  powder X-ray diffractometer

(Ex. 6, Byrn et al., “The X-Ray Powder Diffraction Method”, SSCI, p. 59 (1999)).

42. By measuring the diffraction angles (degrees  $2\theta$ ) and intensities of X-rays diffracted from a given sample, the angle values can be plotted against the differing intensities as “lines” or “peaks” to produce an “X-ray diffraction pattern,” or “powder pattern.” An X-ray diffraction pattern is considered to be the fingerprint of the crystal structure of a material. Thus, XRPD may be used to identify solid state forms of a compound.

43. XRPD is considered the gold-standard in identifying different crystal forms, because it is relatively straightforward to use and because it gives direct information about the crystalline structure and is known to differentiate between forms well. In order to determine whether a sample contains a given crystalline form, one or more peaks can be compared with a reference powder pattern of a known polymorph. It is important that the peaks chosen are characteristic of the given polymorph, i.e., that the chosen or characteristic peak or peaks do not

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overlap with the peaks of other known polymorphs or other components. Typically, a peak or peaks that are chosen for comparison have higher intensities, but not always, and at any rate, intensities can vary significantly such that there is not a standard quantitative range of variation, whereas  $2\theta$  values typically vary by only  $\pm 0.2^\circ 2\theta$ . (Ex. 7, Remington The Science and Practice of Pharmacy 21<sup>st</sup> ed., Pharmaceutical Press 2011:660-661; Ex. 8, Buhrke et al., “A Practical Guide for the Preparation of Specimens for X-Ray Fluorescence and X-Ray Diffraction Analysis,” Wiley & Sons, 1998:31.)

44. XRPD can be performed on a laboratory X-ray diffractometer (“traditional XRPD”) as pictured in the above schematic or on a synchrotron. The key difference is that a synchrotron uses a much more powerful X-ray beam than a laboratory X-ray diffractometer, so a synchrotron can have greater resolution and/or detection limits. We can call X-ray diffraction via a synchrotron “synchrotron-XRPD,” “s-XRPD,” or simply “synchrotron.” A synchrotron is an electron accelerator that uses synchronized magnetic fields. Synchrotron-XRPD is a high resolution technique that can accurately detect crystalline forms in a sample. Synchrotron-XRPD works by exposing a crystalline structure with synchronized magnetic fields, or high-energy X-ray radiation, whereby the crystalline structure diffracts the high-energy X-rays based on the orientation of the molecules within the unit cell.

45. While traditional XRPD is suitable for structural analysis of many compounds, synchrotron-XRPD helps identify crystalline forms with similar structures in complex mixtures or at low detection levels.

46. In traditional XRPD using a  $\text{CuK}\alpha$  source (as was done for Figure 1 of the ’582 patent), the diffraction pattern gives the position of the diffraction peaks as a function of  $2\theta$ . For



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a synchrotron-XRPD, the resulting data from an analysis need to be converted to a  $2\theta$  scale using Bragg's law to compare the results to data from a traditional laboratory XRPD analysis.

47. Bragg's law is:

$$n \lambda = 2d \sin \Theta$$

From this equation, the following equation can be derived and used to convert the synchrotron data to the  $2\theta$  scale:

$$\Theta_2 = \sin^{-1} \left( \frac{\lambda_2}{\lambda_1} \sin \Theta_1 \right)$$

where  $\lambda_1$  is the X-ray wavelength used in the synchrotron testing (i.e. 0.246789 Å or 1.0008 Å),  $\lambda_2$  is the CuK $\alpha$  wavelength (1.54184 Å),  $\theta_1$  is the measured angle in the synchrotron testing and  $\theta_2$  is the corresponding angle using traditional XRPD.

48. For samples that contain mixtures of different solid forms (or different materials), depending on the XRPD method used, it may be difficult to identify the XRPD signals of a specific solid form from the others in the mixture. For these situations, a preparative (wet chemistry) technique known as fluid density separation (or simply density separation) can be used to remove the components that are causing these overlapping XRPD signals.<sup>2</sup> Density separation is a reliable technique for the “separat[ion] of polymorphs of APIs from one another or from excipients.” (Ex. 9, J.W. Steed, *Chem. Commun.*, 2018, 54, 13175 at 13176.) It has been published in refereed journals, and uses well-established basic chemical principles. (*Id.*; *see also*, Ex. 10, J.L. Atwood, *Cryst. Growth Des.*, 2015, 15, 2874-2877.) The density separation technique physically separates solids that have different densities from each other by

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<sup>2</sup> Samples prepared by density separation are not limited to analysis by XRPD.

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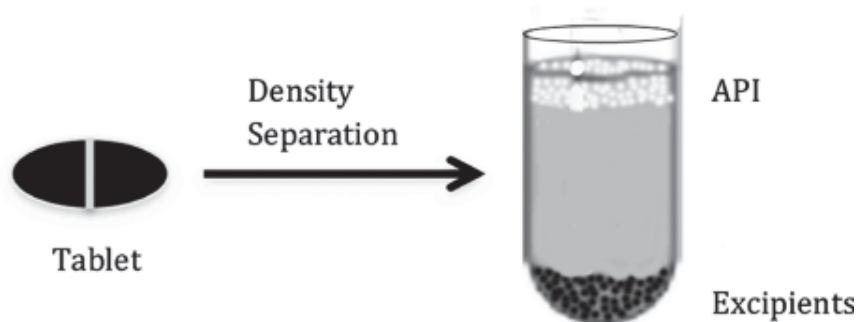
suspending a mixture of solids in a solvent system. The solvent system acts as a medium to segregate different components from the mixture of solids based on differences in density.

49. For example, density separation can separate active pharmaceutical ingredient(s) (“API”) from the other material in a drug tablet (or other pharmaceutical composition) so that it can be analyzed in isolation or with a lower amount of other components. Density separation therefore is a useful preparative technique for the analysis of a specific API solid form of interest in mixtures of other solids.

50. In any density separation procedure, the fluids should be selected such that the material of interest is insoluble in those fluids. Most APIs have densities in the range 1.1–1.5 g/cm<sup>3</sup>, with even more APIs in the narrower range of 1.2–1.4 g/cm<sup>3</sup>. (Ex. 10.) Common crystalline excipients generally fall into two ranges: those with densities over 1.5 g/cm<sup>3</sup> and those with densities less than 1.15 g/cm<sup>3</sup>. (*Id.*) Density separation is performed by adding a solid mixture (containing the analyte) with fluids having different densities, (e.g., mixtures of iodobenzene and hexane), such that the overall solution’s density can be adjusted based on the ratio of the two fluids to separate the component(s) in the solid mixture. In some cases, the sample may be tightly packed and require gentle agitation to free components from each other in the solid mixture. The fluids are also chosen such that the analyte is insoluble in them.

51. As the components are separated from each other, they will segregate based on density. For example, for a pharmaceutical tablet that has been added to a solution of two fluids, the API may float while the excipients may sink to the bottom of the solution. The figure below schematically illustrates results from conducting density separation:

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(*Id.*) Achieving a well-defined separation can require an iterative process. Density separation can also be utilized to separate different solid forms of API contained in the drug tablet (*i.e.* amorphous/crystalline mixtures or crystalline/crystalline mixtures), since different solid forms typically have different densities.

## 2. Raman Spectroscopy

52. Another technique that can be used to identify the crystal structure of a crystalline compound and distinguish between different polymorphs of the same compound is Raman spectroscopy. Raman spectroscopy is a light scattering technique in which a molecule scatters incident light from a high intensity laser light source to provide information about a compound's chemical structure, molecular interactions, and crystallinity. The molecules in a sample will scatter light at different wavelengths. When the light is scattered at the same wavelength as the laser source it is called Rayleigh scattering, and when the light is scattered at different wavelengths, which depend on the chemical structure of the sample, it is called Raman scattering.

53. The results of Raman spectroscopy are displayed as a spectrum, wherein light intensity, expressed as arbitrary units or counts, is displayed on the y-axis, and the frequency of scattered light is expressed as wavenumbers ( $\text{cm}^{-1}$ ) on the x-axis. A Raman spectrum displays a number of peaks that show the intensity and wavelength position of the Raman scattered light.

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Each peak corresponds to a specific molecular bond vibration or a specific functional group vibration.

54. A Raman spectrum can be used to characterize the structure of molecules in a sample and identify the compounds and their environment. Scientists may use Raman spectroscopy to investigate whether a crystalline form of a drug is present in a pharmaceutical dosage form and even to determine if a mixture of crystalline forms are present in a dosage form.

**3. Solid-State Nuclear Magnetic Resonance**

55. ssNMR spectroscopy is used to characterize molecules in a sample by observing local magnetic fields around atomic nuclei. A sample is placed in a strong magnetic field, and irradiated with radio frequency pulses, which can cause nuclei in the sample to resonate. The specific frequency at which the samples resonate depends in part on the local electronic environment surrounding the nucleus. That electronic environment is affected by the compound's functional groups, and in crystalline solids, by the arrangement of molecules in the unit cell. Thus, those local magnetic fields differ between different compounds or between different solid forms of the same compound. ssNMR generates a spectrum for a sample with peaks corresponding to compounds in a sample that generate a signal detected by the ssNMR instrument.

56. ssNMR may be used to characterize the properties of solid materials, such as pharmaceuticals. ssNMR may distinguish crystalline forms versus amorphous forms of a compound. It may also be used to distinguish different crystalline forms of the same compound. Accordingly, ssNMR can be used to detect a particular solid form of a compound in a mixture of other solid forms.

57. Fluorine-19 ( $^{19}\text{F}$ ) ssNMR spectroscopy is a particularly sensitive form of ssNMR.  $^{19}\text{F}$  ssNMR analyzes the local environment around particular atomic nuclei, namely,

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<sup>19</sup>F. <sup>19</sup>F ssNMR only records signals from solid materials that contain <sup>19</sup>F atoms, making it particularly effective for detecting and identifying fluorine-containing compounds and different crystalline forms of fluorine-containing compounds, in addition to distinguishing between crystalline and amorphous materials of fluorine-containing compounds. Because <sup>19</sup>F ssNMR only detects the signal from fluorine-containing compounds, it generates spectra that are relatively easy to read and analyze.

**4. Thermogravimetric Analysis**

58. TGA is a method used to study the desolvation, among other things, of a compound. Desolvation refers to removing solvents, including water, from a sample. TGA can be used to measure the amount of water or solvents, *i.e.*, the mass, in a given sample over time at fixed or varying temperatures. Typically, TGA determines the weight loss of a compound as a function of temperature. This is achieved by placing a pan containing the sample on the balance inside the TGA's oven that is subsequently heated. The weight of the sample is monitored as the temperature is increased inside the oven. As the temperature rises, the solvated sample may desolvate, which is when the solvent molecules escape from the sample as a gas. TGA determines the temperature range over which this occurs and records the weight loss of the sample resulting from desolvation. The results of TGA are often represented in graphical form, in which mass loss (usually from 100%) is displayed on the y-axis and temperature is displayed on the x-axis.

59. For hydrates, the desolvation process is called dehydration, which is the removal of water from the sample. As the temperature of the sample increases, the sample weight decreases due to the loss of water molecules in the crystalline structure. The percentage (%) of weight loss can be used to determine the amount of water lost, which can then be compared to the amount of material remaining. Therefore, TGA can be used to calculate an approximate

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molar ratio of water to compound and characterize the particular type of hydrate — *e.g.*, monohydrate, hemihydrate, or other polymorphic form.

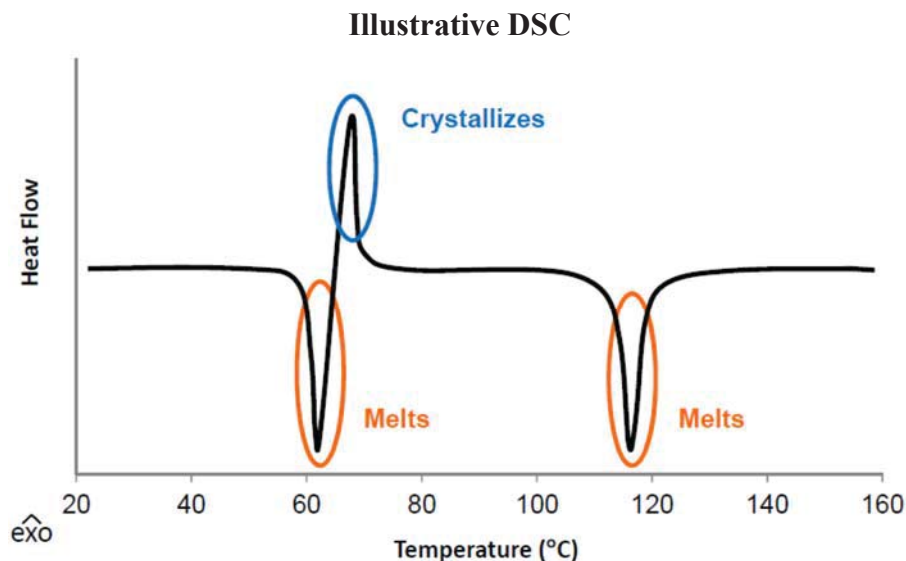
**5. Karl Fischer Analysis**

60. KF is a method used to study the water content of a compound. KF can be used to measure the amount of water in a sample by titrating an anhydrous solution of sulfur dioxide and iodine in the presence of a buffer that reacts with water. (Ex. 11, (USP 26 NF 21 (2003), 2230-2232.) Alternatively, a KF titration can be performed Coulometrically, where the iodine solution is not titrated but rather is produced in an iodine-containing solution by anodic oxidation. (*Id.*) The results of KF water content value is typically reported in % w/w of the total sample added. However, KF is a titration of the total amount of water in a sample and, for example, does not discriminate between surface moisture compared to water bound in a crystalline lattice.

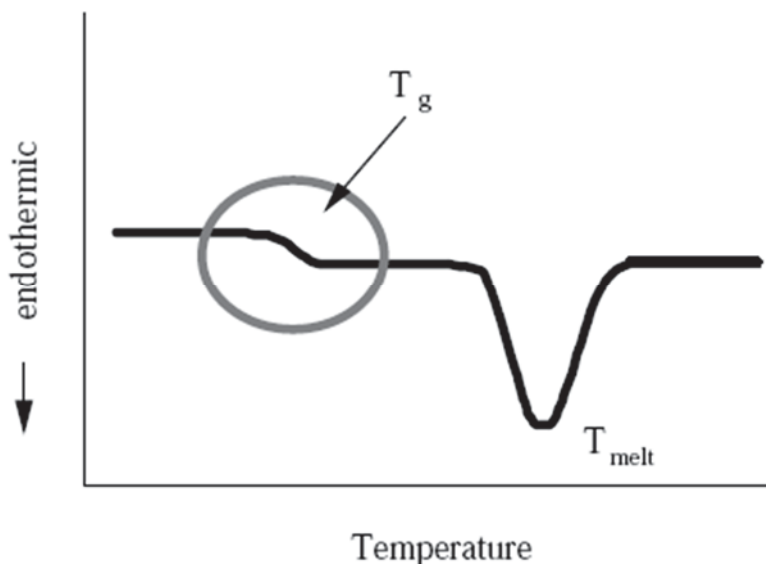
**6. Differential Scanning Calorimetry**

61. DSC is an analytical technique that can be used to ascertain the temperature at which a sample experiences a phase transition or other thermal event. For example, DSC can be used to determine the temperature at which a crystalline solid sample melts to a liquid. Because melting is an endothermic transition—it involves the absorption of energy in the form of heat—one observes a peak, or “endotherm,” on a DSC thermogram when a sample melts. For example, in the hypothetical DSC plot below, the sample melts at about 60 °C (endothermic event, resulting in a downward pointing peak), immediately recrystallizes (exothermic event, resulting in an upward pointing peak), then melts again at about 117 °C (endothermic event, resulting in a downward pointing peak).

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62. It is noteworthy that amorphous compounds undergo a counterpart to melting called a glass transition (the temperature of which is denoted as  $T_g$ ) which is observed as an approximate step change in the DSC thermogram related to the change in heat capacity of a solid vs. a liquid. Thus, this feature is exhibited differently in a thermogram than an endothermic melting point transition. In a sample containing both crystalline and amorphous materials, a DSC thermogram may exhibit both a  $T_g$  and a melt:



## 7. Polarized Light Microscopy

63. Microscopy (visual observation under a microscope) is an analytical technique that can reveal the morphology (size and shape) of the crystals themselves. Polarized light microscopy is a technique that allows one to look for birefringence in a sample, which is indicative of the presence of crystalline material.

### D. Overview of the '582 Patent

64. The '582 patent, entitled "Crystalline form of 1-( $\beta$ -Dglucopyranosyl)-4-methyl-3-[5-(4-fluorophenyl)-2-thienylmethyl]benzene hemihydrate"<sup>3</sup> claims, among other things, a certain solid-state crystalline form of canagliflozin, i.e. crystalline canagliflozin hemihydrate.

65. Claim 1 of the '582 patent recites: "A crystalline form of 1-( $\beta$ -Dglucopyranosyl)-4-methyl-3-[5-(4-fluorophenyl)-2-thienylmethyl]benzene hemihydrate."

66. Claim 3 of the '582 patent recites: "A crystalline form of 1-( $\beta$ -Dglucopyranosyl)-4-methyl-3-[5-(4-fluorophenyl)-2-thienylmethyl]benzene hemihydrate of claim 1, having substantially the same X-ray diffraction pattern as set out in FIG. 1."

67. There are several methods that a POSA may use to characterize solid state crystalline forms of canagliflozin. The '582 patent specifically discloses characterizing the claimed inventions using XRPD, IR, TGA, and/or elemental analysis. (Ex. 4 at 2:63-3:30, 7:11-13.) There are several additional methods that a POSA may use to characterize solid-state forms of canagliflozin and a POSA would not be limited to using only the methods disclosed in the '582 patent. (*Id.* at 2:52-55.)

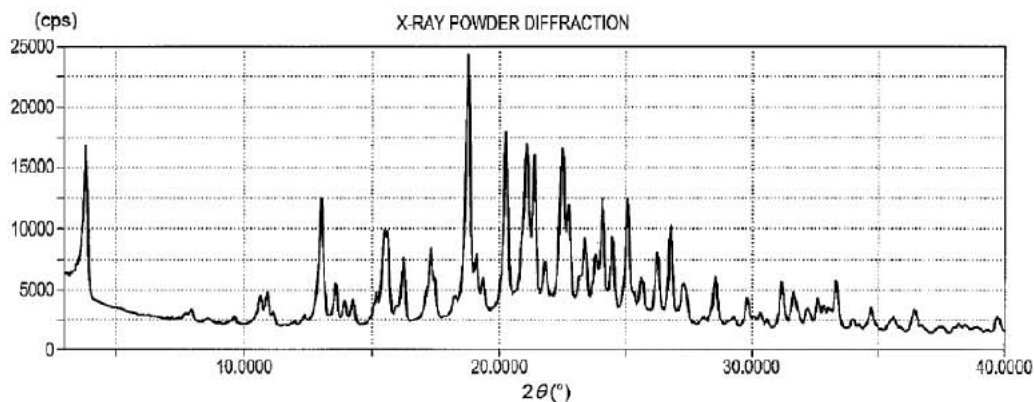
68. The '582 patent discloses a crystalline form of canagliflozin hemihydrate having the XRPD pattern of Figure 1:

---

<sup>3</sup> 1-( $\beta$ -Dglucopyranosyl)-4-methyl-3-[5-(4-fluorophenyl)-2-thienylmethyl]benzene is one of the chemical names for canagliflozin.



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(*Id.* at Fig. 1.)

69. The '582 patent discloses that the crystalline form of the patent “has been observed to exist in a hemihydrate form” and that crystalline canagliflozin hemihydrate has a theoretical water content of 1.98%. (*Id.* at 3:18-22.) The patent further discloses an exemplary TGA showing a mass loss of 1.705%. (*Id.* at 3:22-23.) The reported weight loss of 1.705% translates to a molar ratio of water to canagliflozin of 0.86 to 2 (or 0.43:1) which corresponds to approximately one mole of water to two moles of canagliflozin.

70. In addition, the '582 patent discloses an elemental analysis of the crystalline canagliflozin hemihydrate of Example 1 as follows:

Element	Theoretical	Actual
C	63.56	63.52
H	5.78	5.72
F	4.19	4.08
S	7.07	7.00

(*Id.* at 7:6-13.) Elemental analysis reports the theoretical and actual values in percent by weight for various elements, such as carbon (“C”), hydrogen (“H”), fluorine (“F”), and sulfur (“S”) present in canagliflozin hemihydrate. The actual results of the elemental analysis compared with the theoretical values are consistent with the presence of a hemihydrate.

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71. In my opinion, the data in the patent show that the crystalline canagliflozin form shown in Figure 1 is a hemihydrate.

**E. Claim Construction**

72. I understand that on October 30, 2019, the Court issued an order construing the meaning of certain terms in the asserted claims of the '582 patent. Accordingly, I understand that, for purposes of the asserted patents, the term "crystalline form of canagliflozin hemihydrate" has the meanings ascribed below:

"[C]rystalline form of 1-( $\beta$ -D-glucopyranosyl)-4-methyl-3-[5-(4-fluorophenyl)-2-thienylmethyl]benzene hemihydrate," as it appears in claims 1 and 3 of the '582 Patent, means "a crystalline form of 1-( $\beta$ -D-glucopyranosyl)-4-methyl-3-[5-(4-fluorophenyl)-2-thienylmethyl]benzene comprising approximately half a mole of water to one mole of the compound."

(Ex. 12, Markman Order.)

73. I have considered and applied the Court's Claim Construction in my analysis of the '582 patent. To the extent any terms of the claims have not been construed by the parties or the Court, I understand that those claim terms should be interpreted as they would have been understood by POSA as of December 4, 2006 or December 3, 2007.

74. I have been informed that the Court rejected a proposed interpretation of the claim term "crystalline form of canagliflozin hemihydrate" that would have placed additional limitations on the claims by requiring the term to include the XRPD pattern of Figure 1, the IR spectrum of Figure 2, and a TGA value of 1.705% w/w.

75. A POSA would understand claim 1 of the '582 patent to claim crystalline canagliflozin hemihydrate without any limitation as to the characterization method. In my opinion, and as discussed in further detail below, there are many ways to identify, detect, and/or

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characterize crystalline compounds such as crystalline canagliflozin hemihydrate, including (without limitation) XRPD, sc-XRD, Raman spectroscopy, IR spectroscopy, DSC, and/or TGA.

**F. Characterization of Crystalline Canagliflozin Hemihydrate**

76. For a compound that has already been the subject of extensive research and development with respect to the solid state, a POSA can use basic analytical testing to identify whether or not a given polymorph is contained within a particular sample. Such testing can consist of a single analytical method.

77. Canagliflozin has been found to exist in several crystalline forms. (See Ex. 4; Ex. 13; JSN-INV-00021232 at 3-4.) [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED] In addition, the full 3-D crystal structure of crystalline canagliflozin hemihydrate has been determined using sc-XRD. (See Ex. 14, Liu et al., "Crystal Structure of Canagliflozin Hemihydrate," *Acta Cryst.* (2016) . E72, 734-736; see JSN-INV-00027731.)

[REDACTED]

[REDACTED]

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4 [REDACTED]

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[REDACTED]

79. XRPD is considered the gold-standard in identifying the presence of different crystal forms. A material's XRPD pattern is considered the fingerprint for that solid state form. Figure 1 of the '582 patent is an XRPD pattern of a sample of a crystalline canagliflozin hemihydrate and is the fingerprint for that solid state form. Thus, an XRPD pattern for a sample can be compared to the XRPD pattern of Figure 1 of the '582 patent to identify if that sample contains crystalline canagliflozin hemihydrate.

80. [REDACTED]

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5 [REDACTED]

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[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

81. [REDACTED]

[REDACTED]

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[REDACTED]

[REDACTED]

82. As stated above, Figure 1 of the '582 patent characterizes the compound of Figure 1 as crystalline canagliflozin hemihydrate. Crystalline canagliflozin hemihydrate also has been characterized in the '582 patent based on TGA and elemental analysis. [REDACTED]

[REDACTED]

[REDACTED]

83. [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

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[REDACTED]

84.

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

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[REDACTED]

86. [REDACTED]

[REDACTED]

**G.** [REDACTED]

87. In this report, I examine the data for Zydus's ANDA Products. Specifically, I review the data for Zydus's proposed generic versions of Invokana<sup>®</sup> as described in Zydus's '541 ANDA and Invokamet<sup>®</sup> as described in Zydus's '542 ANDA. I have also reviewed and analyzed certain analytical testing data conducted on samples from representative batches of Zydus's API and its ANDA Products.

88. Zydus's ANDA Products for the '541 ANDA include two dosage strengths—a 100 mg tablet and a 300 mg tablet. (*See* ZYDUS-INVOKA 00023338.) Zydus's ANDA states that the API in Zydus's '541 ANDA Products is canagliflozin. (*Id.*) Zydus's '541 ANDA Products comprise a mixture of ingredients that includes the active ingredient canagliflozin (as discussed above), [REDACTED]

[REDACTED]



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89. The APIs in Zydus's '542 ANDA Products are canagliflozin and metformin hydrochloride. (ZYDUS-INVOKA 00000737; 00000764.) Zydus's ANDA Products for the '542 ANDA include four dosage strengths—a 50 mg/500 mg tablet, a 50 mg/1000 mg tablet, a 150 mg/500 mg tablet, and a 150 mg/1000 mg tablet (the dosages are expressed as canagliflozin/metformin hydrochloride). (ZYDUS-INVOKA 00000737.) Zydus's '542 ANDA Products comprise a mixture of ingredients that includes the active ingredient canagliflozin (as discussed above), [REDACTED]

[REDACTED]

[REDACTED]

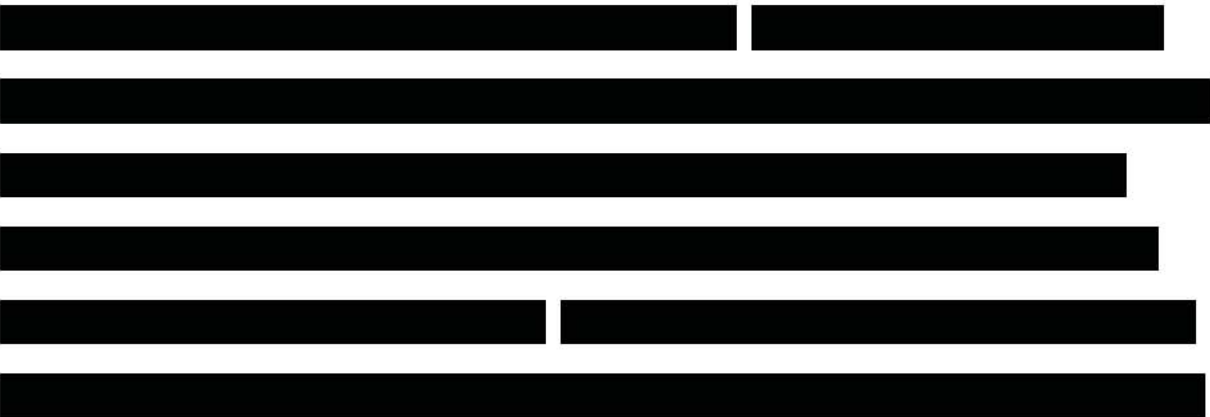
[REDACTED]

[REDACTED]

90. Testing was conducted on Zydus's canagliflozin API and/or ANDA Products by Dr. Fabia Gozzo, Dr. Geert Behets, Dr. Fritz Blatter, Dr. David Atwood, and Dr. Eric Munson. In addition to reviewing the data generated by the analytical testing conducted by those experts and discussed in more detail below, I reviewed the procedures that were followed in storing, shipping, and handling the representative samples produced by MSN in this case of its API and ANDA Products as well as any samples provided by Plaintiffs. In particular, I reviewed the Declarations of Karen Gushurst describing how the samples were stored and handled by Dr. Gushurst at SSCI. (*See*, Exs. 18-21.) I also reviewed the portions of the reports of Dr. Fabia Gozzo, Dr. Geert Behets, Dr. Fritz Blatter, Dr. David Atwood, and Dr. Eric Munson that describe how the samples were stored and handled in their laboratories. Based on that information, it is my opinion that all of the samples used in the testing discussed in this report

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92. Zydus's '541 and '542 ANDAs state that its ANDA Products contain canagliflozin as an API, which has the chemical formula (1S)-1,5-anhydro-1-[3-[[5-(4-fluorophenyl)-2-thienyl]methyl]-4-methylphenyl]-D-glucitol and the following chemical structure:



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[REDACTED]

93. [REDACTED]

94. [REDACTED]

95. [REDACTED]

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[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

96. [REDACTED]

[REDACTED]

[REDACTED]

2. [REDACTED]

97. [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

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[REDACTED]

98. [REDACTED]

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99. [REDACTED]

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100. [REDACTED]

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101.

[REDACTED]

102.

[REDACTED]

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[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

103. [REDACTED]

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3. [REDACTED]

104. [REDACTED]

[REDACTED]

[REDACTED]

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105. [REDACTED]

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106.

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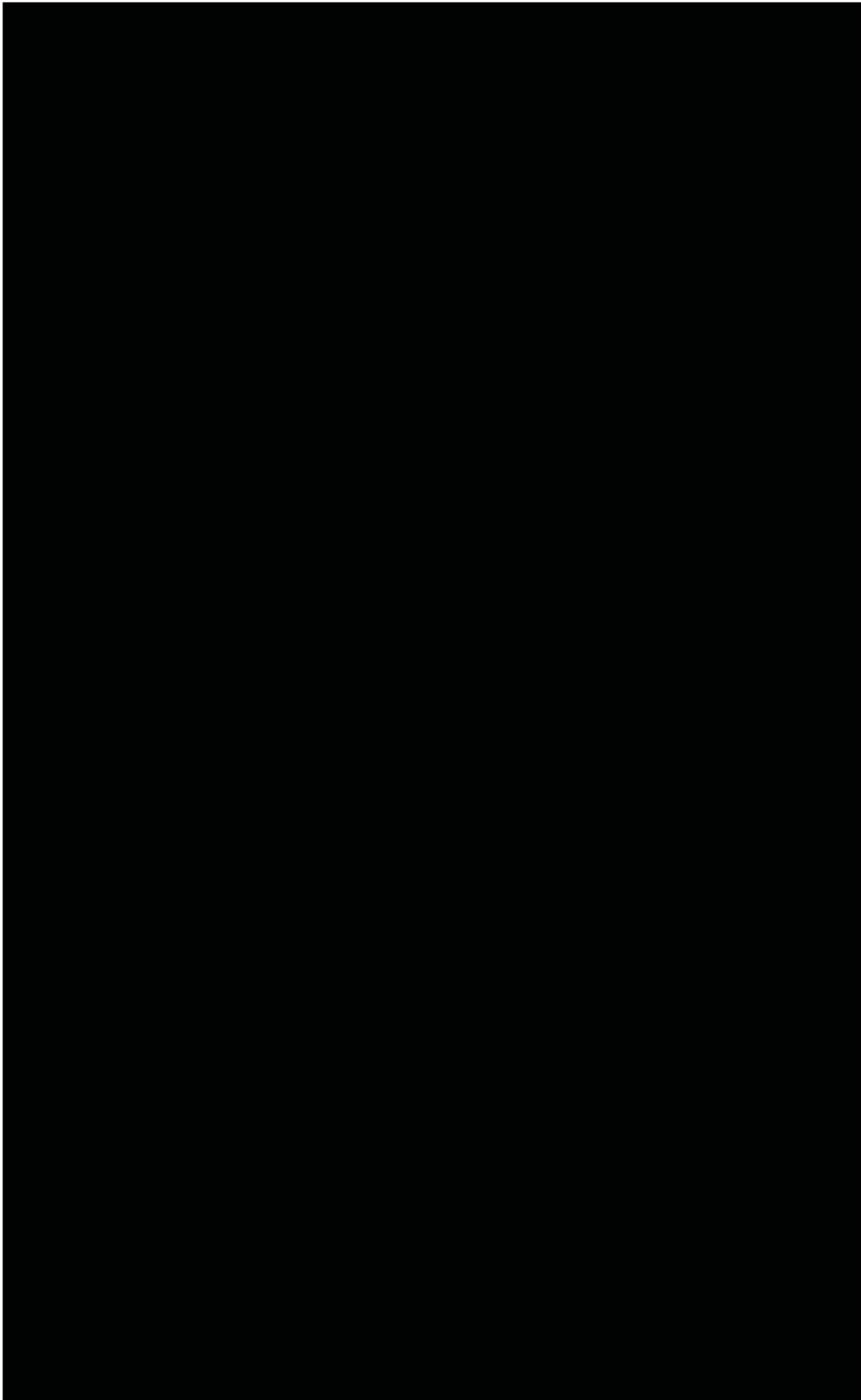


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107. [REDACTED]

[REDACTED]

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[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

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[REDACTED]

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[REDACTED]

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[REDACTED]

[REDACTED]

108. [REDACTED]

[REDACTED]

4. [REDACTED]

(a) [REDACTED]

109. [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

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[REDACTED]

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[REDACTED]

[REDACTED]

[REDACTED]

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110.

[REDACTED]

[REDACTED]

111.

[REDACTED]

(b)

[REDACTED]

112.

[REDACTED]

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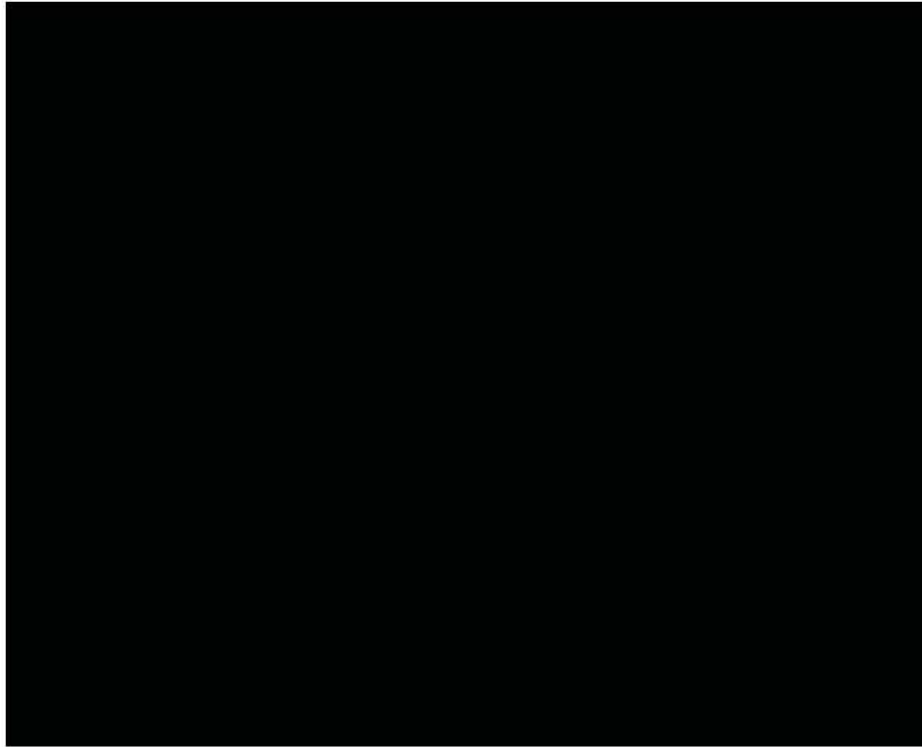
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121.

[REDACTED]

122.

[REDACTED]

[REDACTED]

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[REDACTED]

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123. [REDACTED]

[REDACTED]

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[REDACTED]

124. [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

**(iii)  $^{19}\text{F}$  ssNMR Testing**

125. Furthermore, analytical testing was performed by Dr. Eric Munson to examine the composition of Zydus's canagliflozin API using  $^{19}\text{F}$  ssNMR. Dr. Munson is an expert in the field of  $^{19}\text{F}$  ssNMR and is the type of person that scientists, like myself, would rely on in connection with  $^{19}\text{F}$  ssNMR analysis. I am relying on Dr. Munson's ssNMR expertise in forming my opinions here.

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

51

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[REDACTED]

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[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

(b)

[REDACTED]

136. Further analytical testing was performed to examine Zydus's ANDA Products composition using synchrotron-XRPD, XRPD with density separation, and  $^{19}\text{F}$  ssNMR. I have reviewed the expert reports of Dr. Geert Behets (Ex. 32, the "Behets Rpt."), Dr. Fabia Gozzo (Ex. 33, the "Gozzo Rpt."), Dr. David Atwood (Ex. 34, the "Atwood Rpt."), and Dr. Munson (Ex. 21, the "Munson Rpt."). I have reviewed each of those reports, including the methodology, underlying data, and results, and it is my opinion that the analytical testing was appropriately performed and that the resulting data are correct and accurate. [REDACTED]

[REDACTED]

[REDACTED]

(i)

[REDACTED]

137. Dr. Geert Behets and Dr. Fabia Gozzo performed s-XRPD testing on Zydus's ANDA Products. I have analyzed the data of Zydus's ANDA Products by synchrotron. [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

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[REDACTED]

[REDACTED]

[REDACTED]



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140. [REDACTED]

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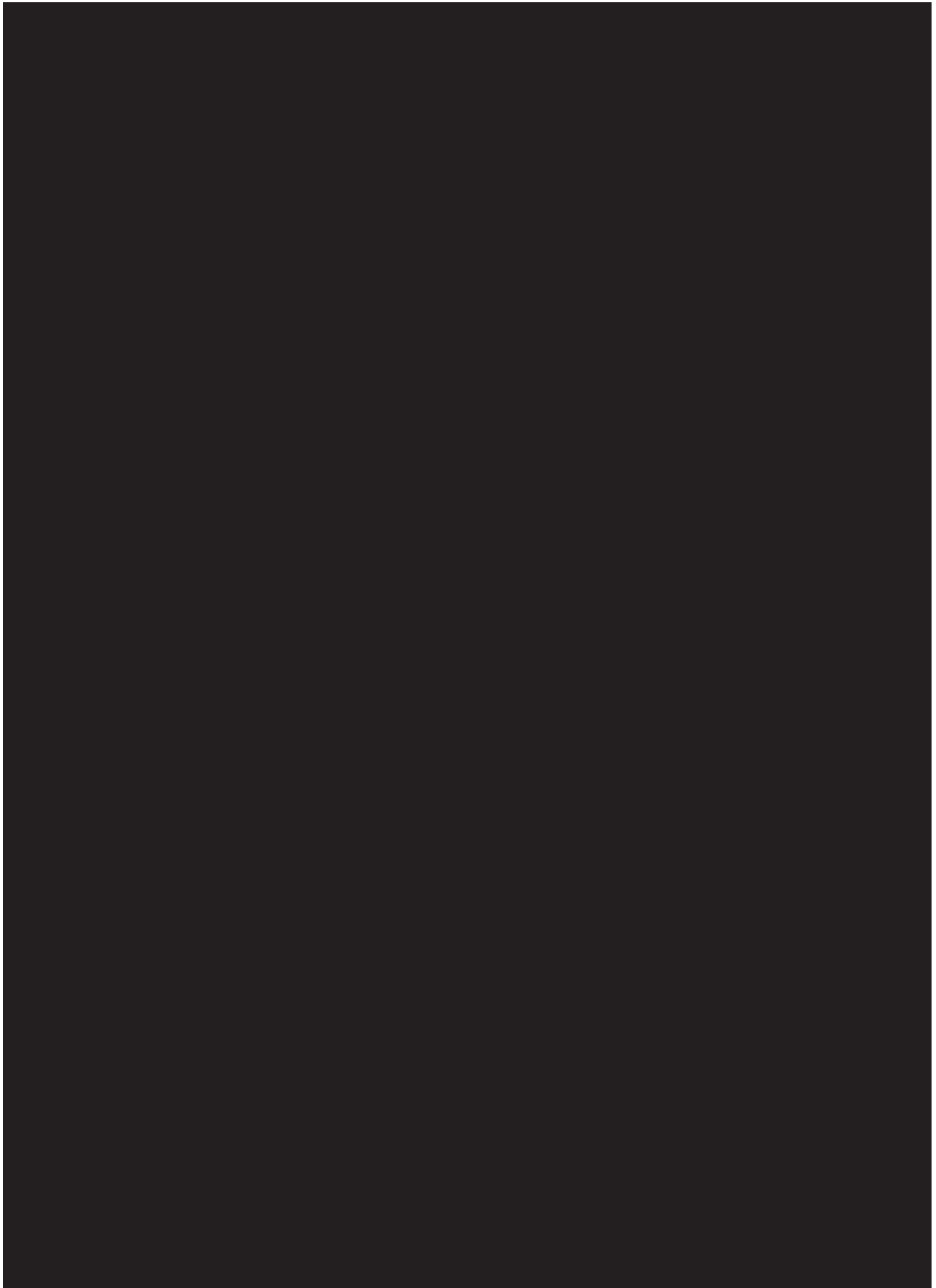
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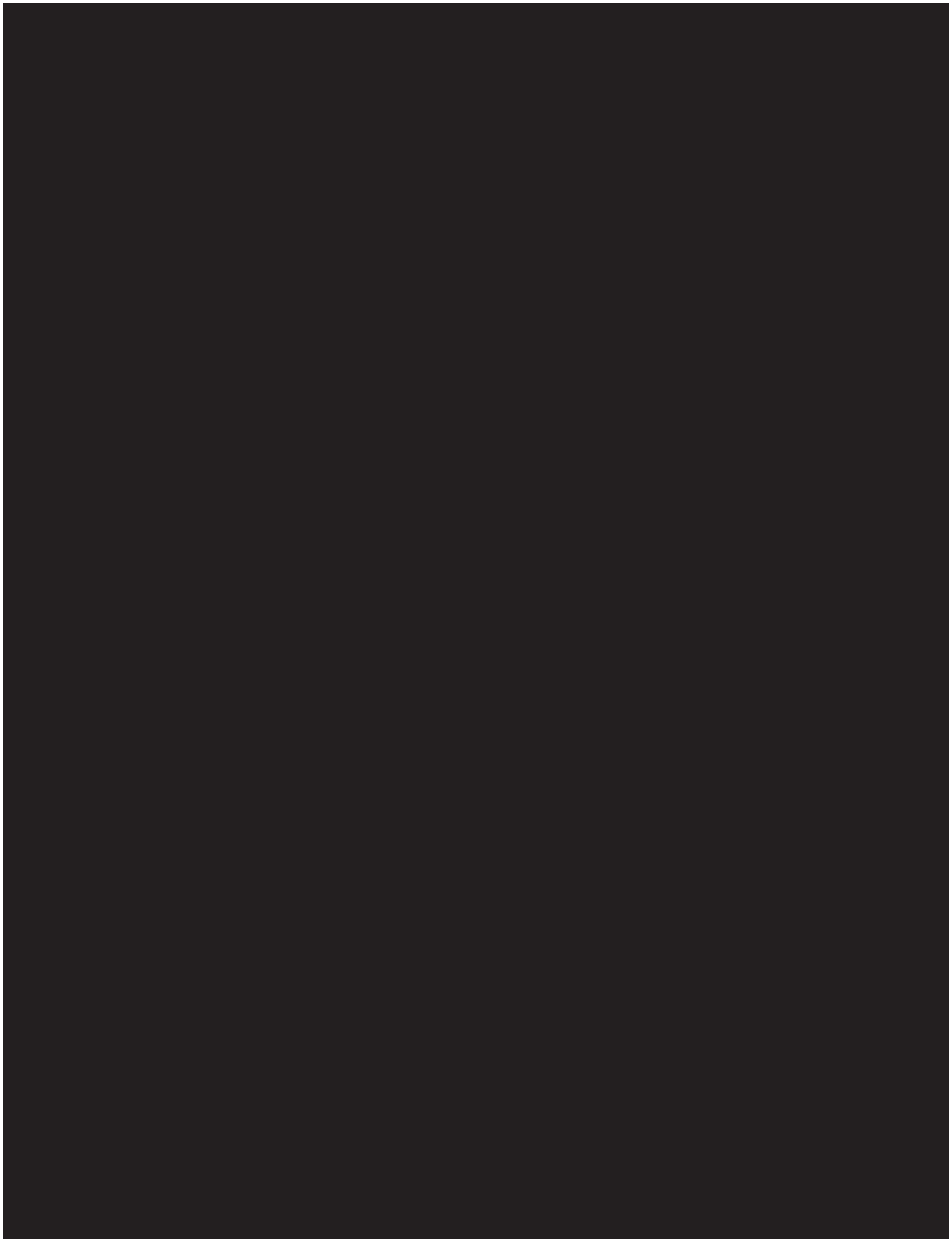
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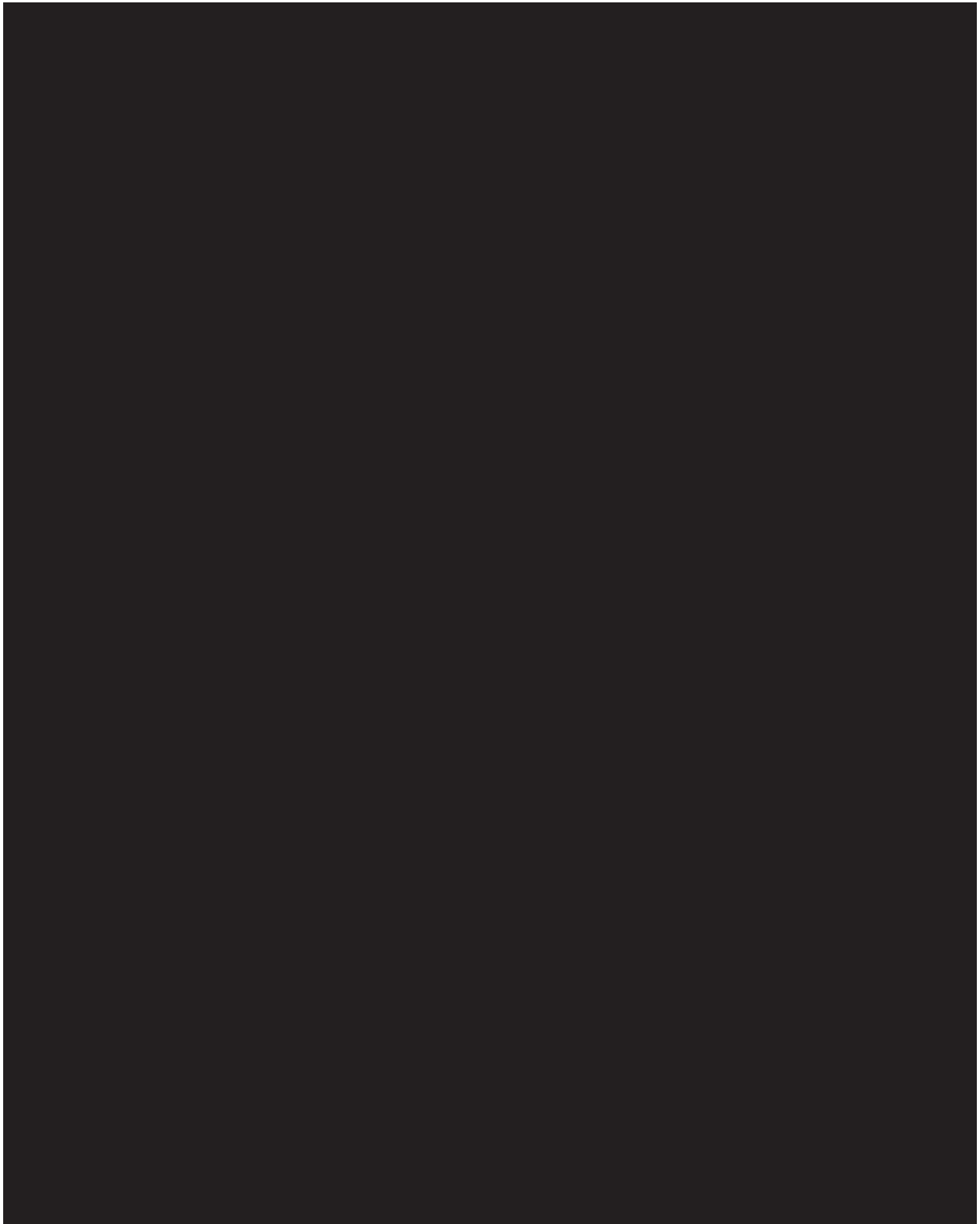
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141. [REDACTED]

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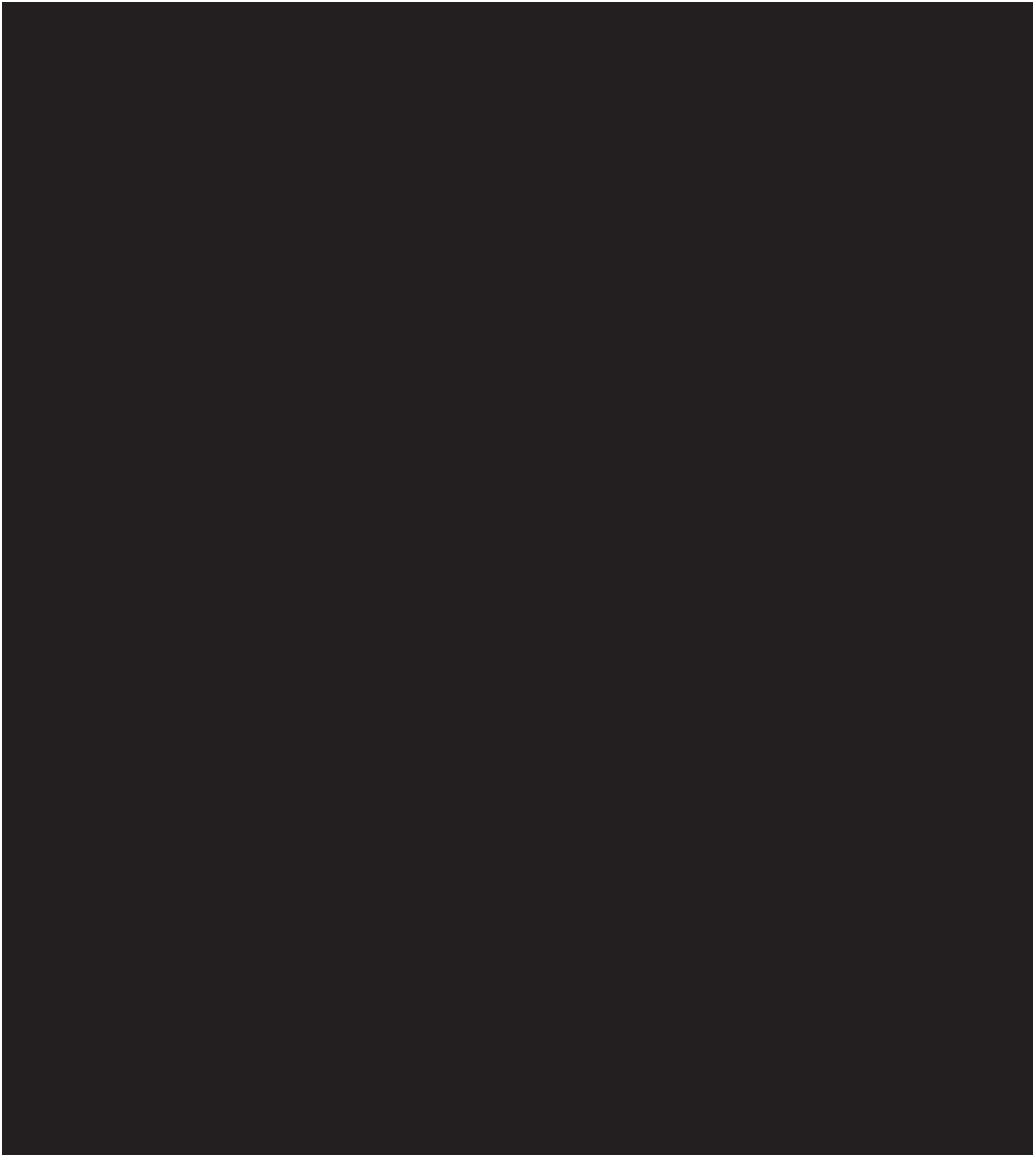
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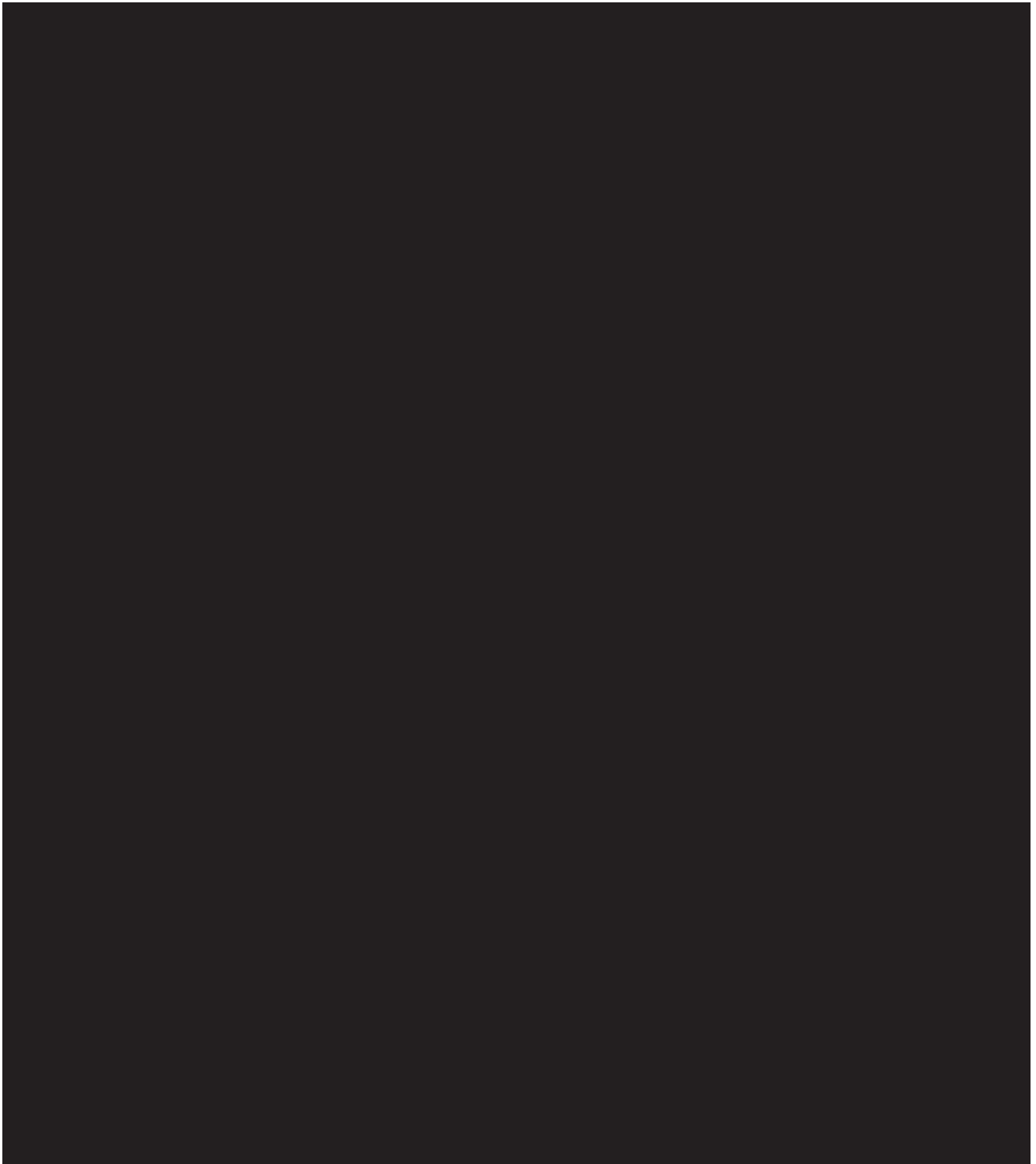
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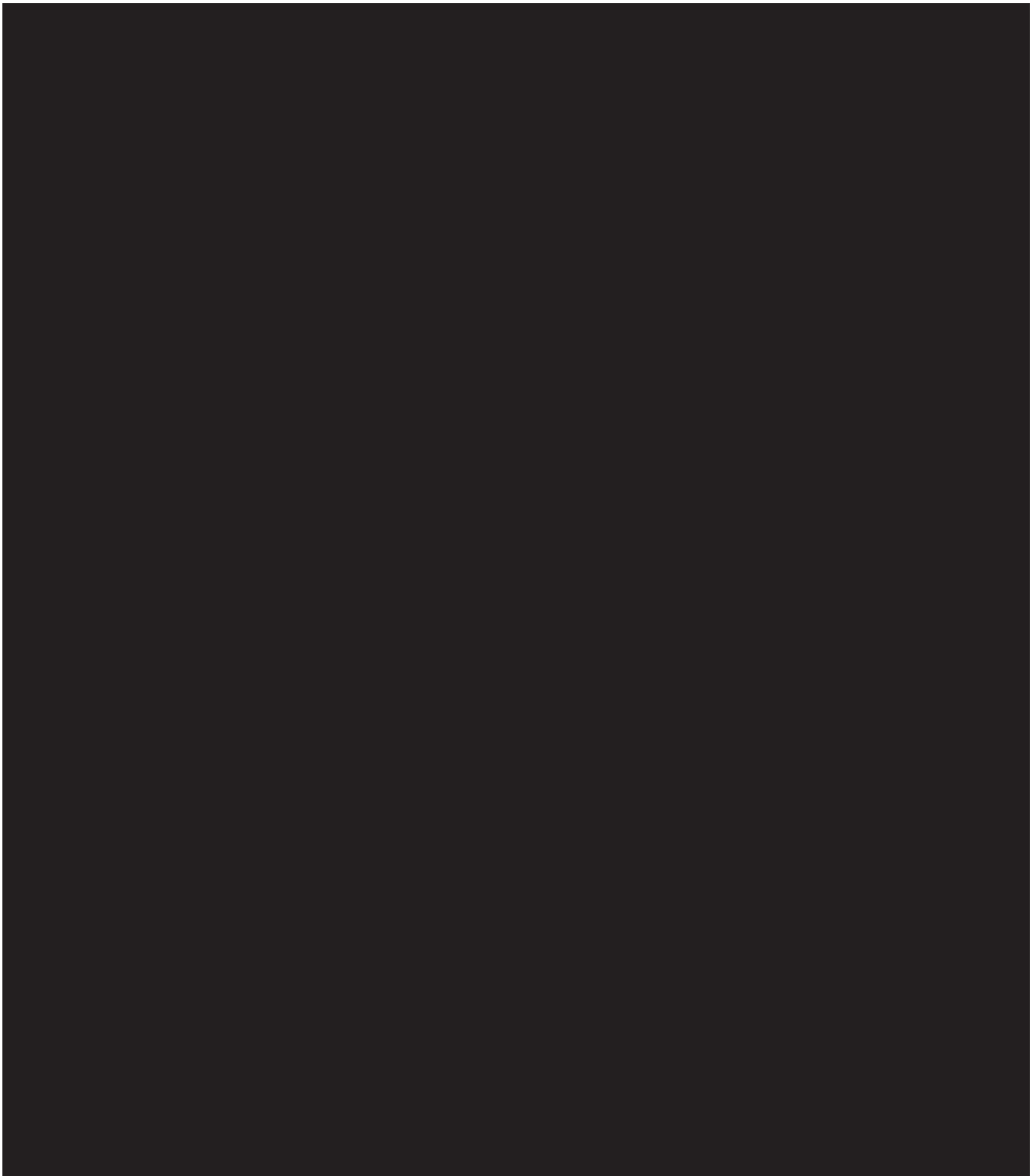


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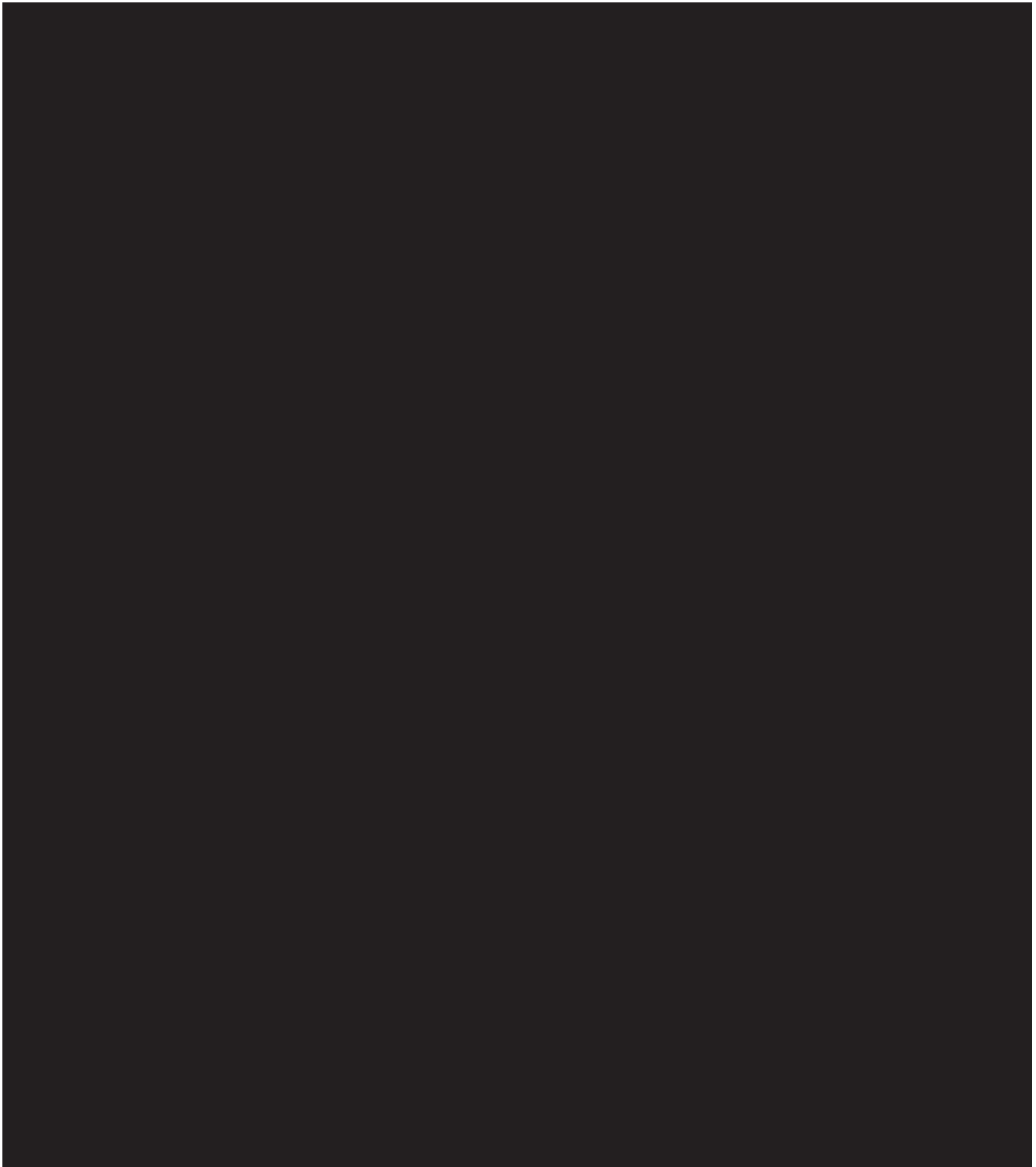




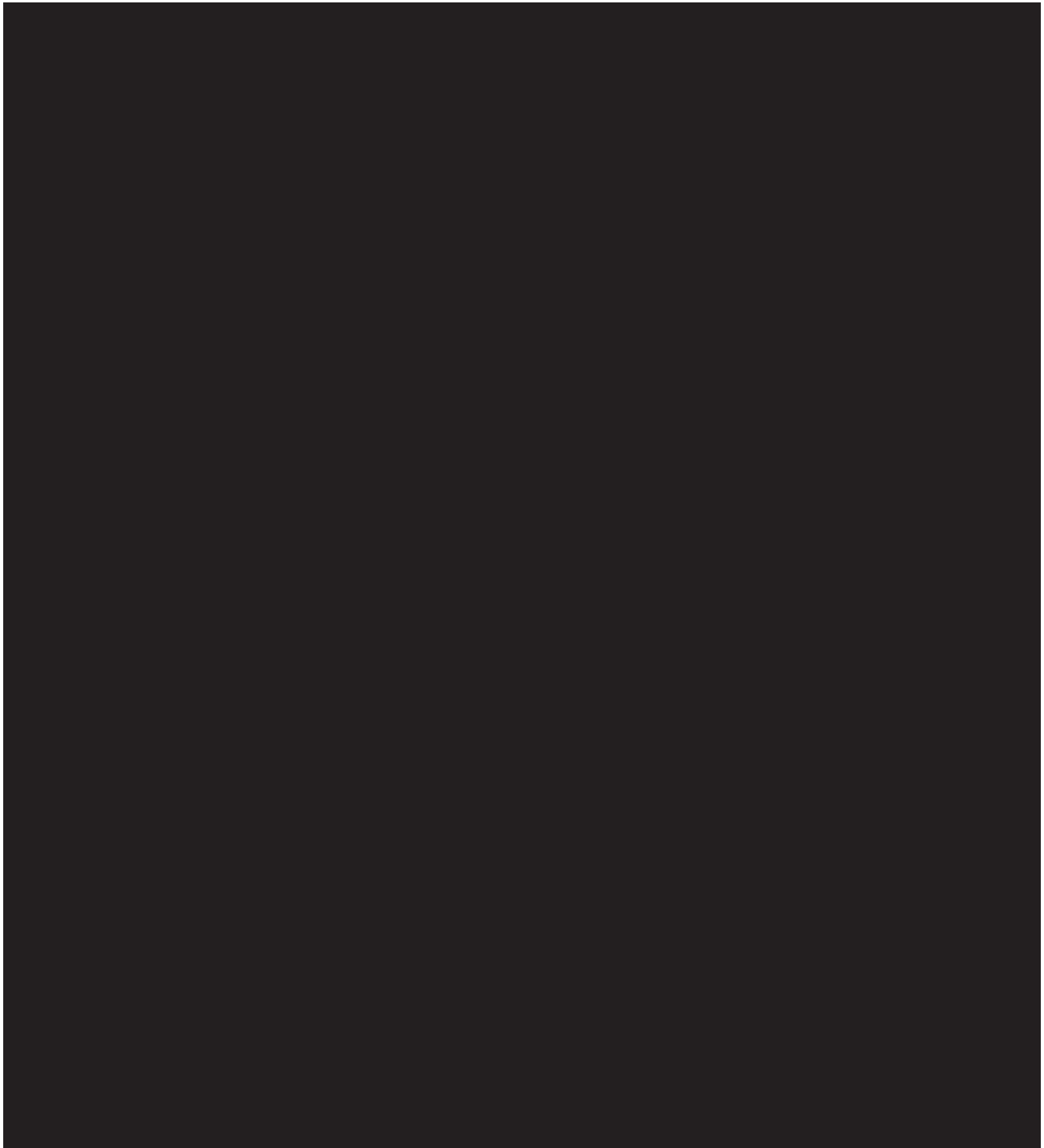
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[REDACTED]

[REDACTED] In my opinion,

[REDACTED]

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[REDACTED]

[REDACTED]

[REDACTED]

143. I also analyzed the full XRPD patterns and peak lists for each of the samples Dr. Behets and Dr. Gozzo tested. (Exs. 32-64.) [REDACTED] [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

144. [REDACTED]

[REDACTED] [REDACTED]

[REDACTED]

[REDACTED]

**(ii) XRPD Testing with density separation**

[REDACTED]

[REDACTED] [REDACTED]

[REDACTED] [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

146. [REDACTED]

[REDACTED]

[REDACTED]

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[REDACTED]

[REDACTED]

[REDACTED] (*Id.* at

3.) [REDACTED]

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[REDACTED]

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[REDACTED]

[REDACTED] (*Id.* at

6.) [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

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### (iii) $^{19}\text{F}$ ssNMR Testing

150. Furthermore, analytical testing was performed by Dr. Eric Munson to examine the composition of Zydus's ANDA Products using  $^{19}\text{F}$  ssNMR. As I stated above, Dr. Munson is an expert in the field of  $^{19}\text{F}$  ssNMR and is the type of person that scientists, like myself, would rely on in connection with  $^{19}\text{F}$  ssNMR analysis. I am relying on Dr. Munson's ssNMR expertise in forming my opinions here.

[illegible]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

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[REDACTED]

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[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]



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**V. SUPPLEMENTATION**

162. I reserve the right to supplement or amend my opinions in response to opinions expressed by Zydus's experts, or in light of additional evidence, testimony, discovery, or other information that may be provided to me after the date of this report.

163. I also reserve the right to offer additional testimony, if necessary, concerning the subject matter of the '582 patent.

164. In addition, I expect that I may be asked to consider and testify about issues that may be raised by Zydus's fact witnesses and technical experts at trial or in their reports. It may also be necessary for me to supplement my opinions as a result of ongoing discovery, Court rulings and testimony at trial.

**VI. TRIAL EXHIBITS**

165. I may rely on visual aids and demonstrative exhibits that demonstrate the bases for my opinions. These visual aids and demonstrative exhibits may include, for example, interrogatory responses, deposition testimony and exhibits, as well as charts, photographs, diagrams, videos, and animated or computer-generated videos.

**HIGHLY CONFIDENTIAL**

**VII. CONCLUSION**

166. As set forth above, it is my opinion that Zydus's ANDA Products will literally infringe claims 1 and 3 of the '582 patent.

Executed this 7<sup>th</sup> day of February 2020, I declare under penalty of perjury that the foregoing is true and correct.

A handwritten signature in blue ink, appearing to read "Bernhard L. Trout", is written above a horizontal line.

Bernhardt L Trout, Ph.D.